concentration over the exposure duration (averaged over a year or more), and are not intended to be compared to a 24-hour average concentration (US EPA, 2010[5]). The annual average TSP values for the three monitoring stations (maximum of 2.48 $\mu g/m^3$)[6] are much lower than the 24-hour (maximum of 25 $\mu g/m^3$ at the Water Plant monitoring station) or monthly (maximum of 6.8 $\mu g/m^3$) averages. Therefore, comparisons of 24-hour and monthly averages to chronic Mn toxicity criteria overestimate potential risks from Mn. Further, as discussed in the previous section, the Mn concentrations reported in the HC include both respirable and non-respirable Mn. Considering only the estimated annual average PM_{10} concentrations (as discussed in Section 2.2, based on estimates of the fraction of PM_{10} in TSP) results in Mn concentrations that are less than, or only slightly greater than, the draft ATSDR MRL of 0.3 $\mu g/m^3$.

As an example of how comparisons to 24-hour averages in the HC overestimate risks, the HC notes that "The range of daily concentrations of manganese detected at the Water Plant is within the lower range of those reported in occupational studies of chronic exposures." The HC appears to be comparing the maximum 24-hour TSP Mn concentrations measured at the Water Plant (25 $\mu g/m^3$) to the lowest chronic value they list for subtle neurological effects in occupational studies (27 $\mu g/m^3$) (note that 25 $\mu g/m^3$ is below, and not within, this range). Our first argument with this statement is that the source of the 27 $\mu g/m^3$ value is not provided by ATSDR and is unclear since the occupational studies consistently indicate that neurological effects are not associated with exposures at or below 60 $\mu g/m^3$ (see Appendix A). Secondly, comparison of a chronic exposure level to a 24-hour measurement is not appropriate. As shown in Table 1 of Appendix B in the HC (for the year where the 24-hour maximum TSP Mn concentration was 25 $\mu g/m^3$), the annual average concentration was more than ten times lower (2.2 $\mu g/m^3$), and well below concentrations where subtle neurological effects have been observed in occupational studies (greater than 60 $\mu g/m^3$, see Appendix A).

Furthermore, if the data in Table 1 of Appendix B of the HC are averaged from 1999-2009 to estimate a 10-year chronic exposure concentration, the concentration is 1.63 $\mu g/m^3$ TSP Mn, which, if one estimates the PM_{10} fraction (as discussed in section 2.2), results in an estimated long-term average chronic respirable exposure concentration equal to the draft ATSDR MRL of 0.3 $\mu g/m^3$. Comparisons of toxicity criteria to long-term averages and annual averages[7] are critical to evaluating potential risks from Mn.

[5] See definition for chronic exposures. Chronic exposures are defined as "Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans," which is typically considered to be more than 7 years.
[6] Note that the maximum annual average TSP Mn concentration (2.48 $\mu g/m^3$) was from more than 10 years ago (1999).
[7] Annual averages are important for considering subchronic risks, *i.e.*, from subchronic exposures that are "more than 30 days, up to approximately 10% of the life span in humans" (US EPA, 2010).

2.1.3 Use of more current toxicity information on Mn results in higher toxicity criteria values that are still health protective

2.1.3.1 Overview of chronic inhalation toxicity criteria

Chronic inhalation toxicity criteria are estimates of continuous inhalation exposure concentrations for individuals (including sensitive subgroups) that represent negligible, if any, risk for adverse health effects during a lifetime (US EPA, 2010). Regulatory agencies have different names for such criteria, although the values are derived using similar methodologies and are applied similarly in making decisions to manage risks from chemicals. For example, the US EPA inhalation criteria are termed as "RfCs;" ATSDR inhalation criteria terms them as "MRLs;" and California EPA inhalation criteria term them as "reference exposure levels (RELs)." These toxicity criteria are established based upon policy decisions to purposely set criteria well below any level in which observable adverse human health effects can be identified. For example, the current US EPA Mn RfC (0.05 $\mu g/m^3$) is set at a level which is 3000 times lower than the level in which subtle neurological effects have been observed (US EPA, 1993).

These toxicity criteria are derived from scientific studies in animals or humans, using either no observed adverse effect levels (NOAELs) (*i.e.*, exposure levels at which no statistically significant increases in adverse effects are observed between exposed and unexposed populations), or on lowest observed adverse effect levels (LOAELs) (*i.e.*, the lowest exposure levels where significant effects have been observed). Toxicity criteria are typically derived by dividing the NOAELs or LOAELs by uncertainty factors (UFs) to account for various uncertainties in the studies used as the basis of the toxicity criteria. Agency policy is typically to use a reliable NOAEL if one is available. Thus, as noted above, inhalation toxicity criteria are developed to be well below concentrations that have been observed to cause adverse health effects.

2.1.3.2 Mn chronic inhalation toxicity criteria

In 1993, US EPA published an RfC of 0.05 $\mu g/m^3$ for Mn. As described in their Integrated Risk Information System (IRIS) summary for Mn (US EPA, 1993), the RfC is based on observations of subtle neurological effects in workers exposed to an average of 150 $\mu g/m^3$ respirable Mn for an average of 5.3 years (Roels *et al.*, 1992).[8] The IRIS summary defines the exposure concentration of 150 $\mu g/m^3$ as the LOAEL from the study. To derive the RfC, US EPA adjusted the LOAEL (which was based on a typical

[8] Note that manganese is not considered a human carcinogen by US EPA (1993).

occupational exposure timeframe of 5 days/week, 8 hours/day) to reflect continuous exposure over a lifetime (7 days/week, 24 hours/day, for 70 years)[9], and then divided this value by UFs (a total UF of 1000) to account for:

- Sensitive populations (UF=10);
- Use of a LOAEL as opposed to a NOAEL (UF=10); and,
- Database limitations, including the use of a subchronic study (less than 7 years in duration), lack of developmental data, and potential differences in toxicity of different forms of manganese (*e.g.*, Mn oxides *vs.* Mn sulfates) (UF=10).

Applying these adjustments to the 150 $\mu g/m^3$ LOAEL resulted in an RfC of 0.05 $\mu g/m^3$. Thus, the RfC is 3000-fold lower than the level of Mn at which subtle neurological effects were observed in workers in the study by Roels and coworkers (Roels *et al.*, 1992).

There have been significant developments since the Roels *et al.* study in 1992, including numerous Mn epidemiology and toxicology studies published in the scientific literature that support a re-evaluation of the Mn RfC. These data are summarized in Appendix A, along with a summary of recent proposed and draft Mn inhalation toxicity criteria. Revisions to the Mn RfC would result in a higher value that is still health protective. For example, ATSDR (2008) proposed a draft MRL of 0.3 $\mu g/m^3$. California EPA (OEHHA, 2008) proposed a draft Mn inhalation reference exposure level (REL) of 0.09 $\mu g/m^3$. Bailey *et al.* (2009), in a peer-reviewed publication of which I am a co-author, proposed a revised RfC of 2 – 7 $\mu g/m^3$. Finally, two additional peer-reviewed studies, summarized by Andersen *et al.* (2010) and Clewell (2010), indicate that inhalation of Mn does not result in increased brain concentrations in adults, children, newborns, or fetuses, until the inhaled (PM_{10})[10] concentration exceeds 10 $\mu g/m^3$ (chronic exposure concentration). Since these peer-reviewed studies suggest that brain concentrations are unchanged at exposure concentrations as high as 10 $\mu g/m^3$, it is unlikely that neurological effects will occur below 10 $\mu g/m^3$, providing additional evidence that the recently proposed inhalation toxicity criteria (ATSDR, 2008; OEHHA, 2008; Bailey *et al.*, 2009) are health protective.

It is unclear why ATSDR does not discuss comparisons to its own draft MRL of 0.3 $\mu g/m^3$ (ATSDR, 2008) other than to present the value in Figures 21-23 of the HC as part of a comparison to monthly and 24-hour averages. Comparison to the proposed MRL should have been discussed in the text and should have been given more weight as part of drawing conclusions from the East Liverpool data since the proposed MRL is based on an evaluation of more recent epidemiology and toxicology data. See

[9] 150 $\mu g/m^3$ x 10 m^3/d / 20 m^3/d x 5 days / 7 days = 50 $\mu g/m^3$ (US EPA, 1993).
[10] PM_{10} = particulate matter with diameter of less than or equal to 10 microns

Appendix A.2.1 and A.2.6. In addition, as discussed above in Section 2.1.2, comparisons should be made to annual averages and not 24-hour or monthly averages (US EPA, 2010) as ATSDR did in the HC. The presentation of results in Figures 21-23 is misleading, particularly Figure 23, which shows daily values from the Water Plant monitoring station compared to the current and proposed MRL. Further, as discussed above (Section 2.1.1) and in more detail in Section 2.2, the HC does not consider the respirable fraction of the data, which leads to an overestimate of Mn concentrations in East Liverpool.

The HC needs to incorporate the current available information regarding Mn inhalation toxicity, including ATSDR's own recent draft Mn MRL, in developing conclusions and recommendations for the East Liverpool community. Most importantly, these conclusions should be based on a comparison to the annual average respirable Mn concentrations, using multiple years of data, and not 24-hour or monthly average TSP data, as ATSDR did in the HC which resulted in an overestimate of risk.

2.1.4 Recent Mn occupational epidemiological studies provide a more reliable basis for interpreting ambient Mn data than community studies

Although the HC discusses certain epidemiology studies, several key occupational studies that were available during the time the HC was prepared (discussed in Appendix A of this report), are not presented. In particular, the HC focuses on the less reliable community-based studies as evidence for the ambient Mn concentrations as potentially being associated with neurological effects. As discussed in more detail in Appendix A, community-based studies are understood to be less reliable because such they rely on uncertain exposure characterization with respect to both time, concentration and, typically, a lack of individual-specific data (Webster *et al.* 2007; Gordis, 2008). Occupational studies are generally more reliable for assessing dose-response relationships and should have been given more weight in ATSDR's analysis. In fact, occupational studies (not community-based studies) are the basis of the current and recent Mn inhalation toxicity criteria put forth by ATSDR, US EPA, and California EPA (see Appendix A).

2.2 Mn concentrations in ambient air do not present a toxicological concern for individuals living in the East Liverpool community

As outlined in this Section, the use of more appropriate annual average respirable air concentrations and current Mn toxicity data indicates that Mn in ambient air does not present a toxicological concern for individuals living in the East Liverpool community. Further, without adequate

analysis of background concentrations of Mn in this community, the HC inappropriately focuses on S.H. Bell Company.

2.2.1 The estimated annual average Mn PM_{10} concentrations are well-below Mn TSP concentrations and are more appropriate for use in comparison to Mn inhalation toxicity criteria

To evaluate potential human health risks from Mn in ambient air in the East Liverpool community, I reviewed the 1999-2009 annual average TSP Mn concentrations presented in Appendix B of the HC (ATSDR, 2010). In addition, I reviewed 2010 average TSP Mn ambient air data (January – September 2010) from OEPA (OEPA, E. Liverpool Heavy Metals TSP Data, 2010). I also used 2009 (only Q1 data were available) Mn PM_{10} data from the PM_{10} sampler at the Water Plant monitoring station from OEPA to estimate the percent respirable particulate Mn in the TSP data (OEPA, Water Plant Heavy Metals PM10 Data, 2010). Although the respirable fraction is more accurately represented by PM_5 than the PM_{10} fraction (particulate matter with size ranging mostly 5 microns or less) (Klaassen, 2008), and the available PM_{10} data represent only a small timeframe, the PM_{10} data represent a reasonable estimate for the respirable Mn fraction. Additional PM_{10} data (or PM_5) would better confirm Mn concentrations in the respirable fraction.

Fifteen 24-hour Mn PM_{10} samples were collected by OEPA from January – March 2009 at the Water Plant monitoring station. Fifteen data points provide a statistically sufficient dataset for analysis of this time period. The average PM_{10} Mn concentration over that 3-month period was 0.15 $\mu g/m^3$, and the overall average fraction of PM_{10} Mn in the TSP Mn was 20%. Table 1 summarizes the PM_{10} data from OEPA. I applied this 20% estimate to the annual average TSP Mn concentrations to estimate annual average Mn PM_{10} concentrations for each monitoring station, shown in Table 2 [for example: 2.48 $\mu g/m^3$ TSP from 1999 Water Plant x 20% = 0.496 $\mu g/m^3$ estimated PM_{10} concentration].

I compared the estimated annual average[11] Mn PM_{10} concentrations to both the current and proposed Mn RfCs and MRLs. Comparisons from all three monitoring stations are presented in Figure 1.

[11] Although a comparison to annual averages is appropriate, long-term averages should also be considered, and are typically utilized to derive chronic toxicity criteria.

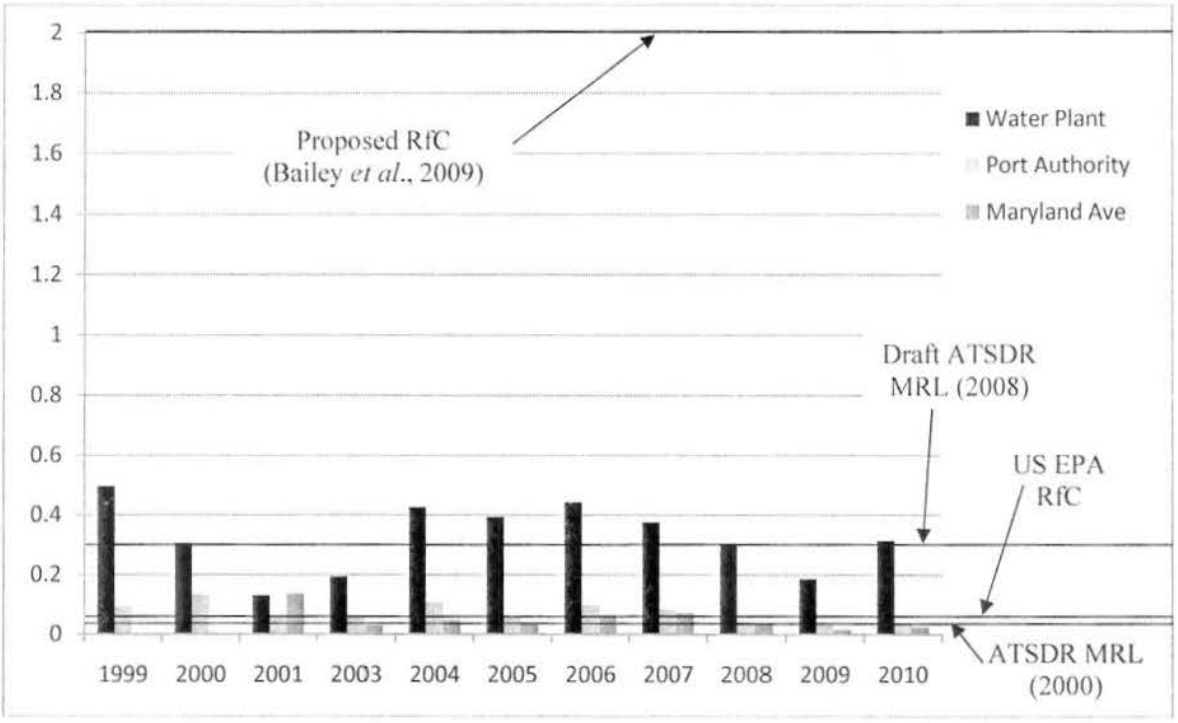

Figure 1 **Estimated Annual Average Mn PM_{10} Concentrations ($\mu g/m^3$) Compared to the Current and Proposed Mn RfCs and MRLs.**

As shown in Figure 1, although some of the estimated annual average PM_{10} concentrations for the Port Authority and Maryland Ave monitoring stations slightly exceed the US EPA RfC and current ATSDR MRL, all air concentrations for these stations are below the draft ATSDR MRL. For the Water Plant monitoring station, some years slightly exceed the draft ATSDR MRL, whereas other years are less than or equal to the draft MRL. All of the values are below the Mn RfC proposed by the peer-reviewed study by Bailey *et al.* (2009), and well below the potential threshold of 10 $\mu g/m^3$ for accumulation of Mn in the brain as also reported in the peer-reviewed study by Andersen *et al.* (2010), and in a recent presentation by Clewell (2010).

In addition, as discussed in section 2.1, if TSP data for each station are averaged over 1999-2010 to estimate an 10-year chronic exposure concentration, the concentration is 1.62 $\mu g/m^3$ TSP Mn, which, if one estimates the PM_{10} fraction (20% of TSP), results in an estimated long-term average chronic respirable exposure concentration equal to the draft ATSDR MRL of 0.3 $\mu g/m^3$. As discussed, comparisons of toxicity criteria to long-term and annual averages are important in evaluating potential risks from Mn.

Furthermore, it is important to consider these concentrations in the context of background concentrations, as discussed above. Background concentrations of Mn in the East Liverpool air can range from 0.03 to 6.2 $\mu g/m^3$ TSP (24-hr average basis), based on examination of Water Plant monitoring station monitoring and meteorological data from 2006 through September 2010 (OEPA, E. Liverpool Heavy Metals TSP Data, 2006 - 2010). The ATSDR HC does not discuss the concentrations in the East Liverpool air in the context of background concentrations. Again, without adequate analysis of background concentrations of Mn in this community, the HC inappropriately focuses on S.H. Bell Company as a potential source.

2.2.2 Because of the health protective assumptions in the RfC and the MRL, exceedances of such criteria should not be taken as evidence of increased risk

While Figure 1 shows some exceedances of the current and draft ATSDR Mn inhalation toxicity values, the majority of the annual average estimated respirable Mn concentrations are below the draft ATSDR MRL, with any exceedances only slightly above the draft value. In this context, it is important to understand the appropriate interpretation of exceedances of chronic toxicity values. Exceedance of a chronic toxicity value (such as an RfC or chronic MRL) does not indicate that any one individual is at elevated risk. That is, chronic toxicity values that include uncertainty factors and assumptions of continuous exposures, such as ATSDR MRL and US EPA RfC, are not intended to be an exact line above which toxic effects will occur and below which no effects will occur. US EPA has explained that toxicity criteria published in their IRIS database cannot be used to predict whether or not an adverse health effect will occur:

> In general, **IRIS values cannot be validly used to accurately predict the incidence of human disease** or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental exposures. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposure to a chemical influence the occurrence and extent of human disease. (US EPA, 2005) [emphasis added]

ATSDR includes a similar discussion in describing MRLs:

> These substance-specific estimates [MRLs], which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that **MRLs are not intended to define clean-up or action levels**...MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor

> approach. They are **below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. Exposure to a level above the MRL does not mean that adverse health effects will occur.** (ATSDR, 2008) [emphasis added]

Therefore, by using the more reliable estimate of concentrations of respirable Mn in ambient air in the East Liverpool community; while considering the more recent and more scientifically supported Mn inhalation toxicity values and potential threshold for increased concentration of Mn in the brain; as well as how one should apply chronic toxicity values to make risk management decisions (*i.e.*, comparison of criteria to annual average concentrations, not 24-hour or monthly averages, and to respirable, not TSP, Mn concentrations), I conclude that Mn concentrations in ambient air do not present a toxicological concern for individuals living in the East Liverpool community.

2.2.3 The estimated multi-year annual average Mn PM_{10} concentrations do not support a need for a survey of neuro-degenerative disease in East Liverpool

ATSDR's conclusions are not consistent with the current understanding of Mn toxicity, nor are they consistent with how chronic toxicity values (RfCs and chronic MRLs) should be applied to risk management decisions. In the HC, ATSDR inappropriately compares 24-hour and monthly TSP Mn concentrations to chronic respirable toxicity criteria, which results in an overestimate of risk from Mn. Instead, based on the East Liverpool ambient air data, there is no sound scientific basis for recommending evaluation of "incidence of neurodegenerative diseases in the East Liverpool community…as an indicator of health impacts from exposure to manganese." Based on the very low concentrations of ambient Mn in the community (no higher than an annual average of 2.5 $\mu g/m^3$ TSP), and considering the estimated annual average concentration in the respirable (PM_{10}) fraction (less than to only slightly greater than the draft ATSDR MRL of 0.3 $\mu g/m^3$, ranging from 0.1 to 0.5 $\mu g/m^3$ at the Water Plant monitoring station), as well as current information on Mn toxicity suggesting that concentrations higher than the RfC (possibly as high as 10 $\mu g/m^3$) are still health protective, Mn concentrations in ambient air do not present a toxicological concern for individuals living in the East Liverpool community. Furthermore, the annual average concentrations need to be considered in the context of typical background Mn TSP concentrations in East Liverpool that range from 0.03 to 6.2 $\mu g/m^3$ TSP (24-hr average basis). Thus, there is no reliable basis for ATSDR's recommendation for a survey of neurodegenerative diseases in the East Liverpool community.

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Tables

Table 1
Water Plant Mn PM_{10} *vs.* TSP Monitoring Data

Date	Mn TSP ($\mu g/m^3$)	Mn PM_{10} ($\mu g/m^3$)	% PM_{10} Mn of TSP Mn
01/01/09		<0.014	
01/07/09		0.071	
01/13/09	0.110	<0.014	<12.73%
01/19/09	0.230	0.036	15.65%
01/25/09	0.081	<0.014	<17.28%
01/31/09	0.052	<0.014	<26.92%
02/06/09	3.400	0.610	17.94%
02/12/09	0.090	<0.015	<16.67%
02/18/09	2.600	0.470	18.08%
02/24/09	1.200	0.260	21.67%
03/02/09	0.490	0.058	11.84%
03/08/09	0.069	0.049	71.01%
03/14/09	0.190	0.017	8.95%
03/20/09	0.370	0.050	13.51%
03/26/09	3.900	0.540	13.85%
Average		**0.149**	**20%**

Table 2
Estimated Annual Average Mn PM_{10} Concentrations ($\mu g/m^3$) at the East Liverpool Air Monitoring Stations

		Water Plant		Port Authority		Maryland Ave	
Year	Estimated % PM_{10} Mn of TSP Mn	TSP	PM_{10}	TSP	PM_{10}	TSP	PM_{10}
1999	0.2	2.48	0.496	0.466	0.0932		
2000	0.2	1.53	0.306	0.669	0.1338		
2001	0.2	0.65	0.13	0.273	0.0546	0.68	0.136
2003	0.2	0.969	0.1938	0.299	0.0598	0.144	0.0288
2004	0.2	2.13	0.426	0.533	0.1066	0.238	0.0476
2005	0.2	1.97	0.394	0.301	0.0602	0.185	0.037
2006	0.2	2.216	0.4432	0.488	0.0976	0.32	0.064
2007	0.2	1.88	0.376	0.433	0.0866	0.359	0.0718
2008	0.2	1.53	0.306	0.219	0.0438	0.171	0.0342
2009	0.2	0.929	0.1858	0.157	0.0314	0.081	0.0162
2010	0.2	1.57	0.314	0.19	0.038	0.12	0.024

Appendix A

Manganese Inhalation Toxicity Criteria

This appendix summarizes the basis of the current Mn RfC (US EPA, 1993), more recent Mn epidemiology and toxicology data, and more recent proposed and draft Mn inhalation toxicity criteria based on the more recent data.

A.1 Current US EPA RfC from 1993

In 1993, the United States Environmental Protection Agency (US EPA) published a Reference Concentration (RfC) of 0.05 $\mu g/m^3$ for manganese (Mn). As described in their Integrated Risk Information System (IRIS) summary for manganese (US EPA, 1993), the RfC is based on observations of subclinical neurological effects in workers exposed to an average (geomean) of 150 $\mu g/m^3$ respirable manganese for an average of 5.3 years (Roels *et al.*, 1992). The IRIS summary defines the exposure concentration of 150 $\mu g/m^3$ as the LOAEL from the study. To derive the RfC, US EPA adjusted the LOAEL to reflect continuous exposure over a lifetime (7 days/week, 24 hours/day, for 70 years)[12], and then applied uncertainty factors (UFs) to account for: sensitive populations (UF=10); use of a LOAEL as opposed to a NOAEL (UF=10); and, database limitations, including the use of a subchronic study, lack of developmental data, and potential differences in toxicity of different forms of manganese (UF=10). Applying these adjustments to the LOAEL resulted in an RfC of 0.05 $\mu g/m^3$. Thus, the RfC is 3000-fold lower than the level of manganese at which subclinical effects were observed in workers in the study by Roels and coworkers (Roels *et al.*, 1992).

A.2 More recent proposed and draft Mn inhalation criteria

Since 1993, there have been a substantial number of manganese epidemiology and toxicology, peer-reviewed studies published in the scientific literature that suggest a re-evaluation of the Mn RfC is necessary.

A.2.1 Recent epidemiology data relevant to re-evaluation of the Mn RfC

As summarized in our recent publication where we proposed a revised Mn RfC (Bailey *et al.*, 2009), we identified 12 Mn occupational studies of eight cohorts that were published after 1992 (Table A.1). These studies involved chronic exposure to particulate Mn in air where personal air monitoring data were used to estimate exposure, an unexposed control group was evaluated, and the exposed group was

[12] 150 $\mu g/m^3$ x 10 m^3/d / 20 m^3/d x 5 days / 7 days = 50 $\mu g/m^3$ (US EPA, 1993).

examined for subclinical neurobehavioral effects, predominantly effects on the motor system (typically visual reaction time, hand-eye coordination, and hand steadiness). These peer-reviewed studies are described below.

Additionally, although we describe both respirable and total Mn studies in Table A.1, all recent proposed and draft Mn inhalation toxicity criteria reflect respirable Mn exposure data. The respirable particulate Mn fraction is more biologically relevant than total manganese because respirable Mn particles are capable of penetrating the lung tissue, while larger particles are trapped in the nasal and pharyngeal passages, do not penetrate the lung tissue, and do not enter the circulation (Klaassen, 2008). As shown in Table A.1, five studies evaluated total, rather than respirable, Mn (Chia *et al.*, 1993; Lucchini *et al.*, 1995, 1999; Crump & Rousseau, 1999; Myers *et al.*, 2003). The LOAELs in these studies ranged from 96 to 1,590 $\mu g/m^3$. Since exposures in these studies do not reflect the biologically relevant respirable fraction of particulate Mn, these studies were not considered for re-evaluation of the Mn RfC.

Further, the occupational studies shown in Table A.1 typically report Mn exposure concentrations in arithmetic mean, geometric mean, median, or a combination of these statistics. We consider the arithmetic means to be the most relevant for exposure estimates based on studies suggesting that the arithmetic mean provides a better summarization of group exposure with regard to a dose-response relationship, and is therefore more appropriate for use in risk assessment (Clewell *et al.*, 2003; Crump, 1998). In cases where arithmetic means were not available, we present the geometric mean or median value.

Three chronic studies of respirable Mn were identified from which no observed adverse effect levels (NOAELs) could be derived (Gibbs *et al.*, 1999; Deschamps *et al.*, 2001; Young *et al.*, 2005). Gibbs *et al.* (1999) conducted a study of 75 Mn-exposed workers at an alkaline battery plant in northern Mississippi with no known history of occupational exposure to Mn. The mean Mn air concentration in respirable dust in exposed workers, measured by personal air monitors, was 66 $\mu g/m^3$. The mean exposure duration was 12.7 years. Subjects were administered multiple neuropsychological tests, including hand-eye coordination, hand steadiness, complex reaction time, and rapidity of motion. No significant effects of Mn exposure were found on any neurobehavioral test, indicating in a NOAEL of 66 $\mu g/m^3$.

Deschamps *et al.* (2001) conducted neurobehavioral examinations in 138 enamels-production workers exposed to Mn for an average of 19.9 years and 137 matched technicians from public service

employers or local municipal operations laborers. The mean respirable Mn exposure concentration was 57 $\mu g/m^3$, with a maximum concentration of 293 $\mu g/m^3$ in exposed workers based on personal monitor measurements. The authors conducted several neurological tests, including: sensory and motor exam of cranial nerves; fine-touch, motor, and sensory exam of power of all main muscle groups; reflex tests; cerebellar abnormalities; tests of domains of speech regulation and initiation, attention, concentration and memory, cognitive flexibility, and affect; and a questionnaire for neuropsychological status. Some of the self-reported neuropsychological effects were higher in the exposed group [*i.e.*, asthenia (lack of energy and strength), sleep disturbance, and headache], but the authors indicated that these non-specific symptoms may not be exposure related, based on possible low Mn blood levels in these individuals. Only one neurological test (the visual gestalt test) score was higher in workers exposed to Mn for 11 to 15 years, but the authors attribute this to the higher technical skills of this group of six workers. In addition, there was a lack of a dose-response relationship for this effect, since no statistically significant effects were noted in the four people exposed 16-19 years or the 69 people exposed for 20+ years. Based on these results, the authors concluded that "long exposure to low levels of Mn...showed no significant disturbance of neurological performance." This study indicated a Mn NOAEL of 57 $\mu g/m^3$.

Young *et al.* (2005) conducted a study of 509 South African Mn-exposed smelter workers and 67 unexposed electrical assembly plant workers as the control group. Respirable Mn exposures, from personal samplers, ranged from 3 to 510 $\mu g/m^3$, with a median of 58 $\mu g/m^3$. The authors evaluated several neurobehavioral endpoints, including endpoints from the Swedish nervous system questionnaire (Q16); the World Health Organization neurobehavioral core test battery (WHO NCTB); the Swedish performance evaluation system (SPES); the Luria-Nebraska (LN); the Danish Product Development (DPD) test batteries; and a brief clinical examination. The study found "few respirable Mn effects showing a clear continuity of response with increasing exposure." They observed dose-response associations primarily with exposures less than 100 $\mu g/m^3$, above which the relationship was flat. The authors concluded that the study was essentially negative and that "the small number of convincing effects, especially motor function effects, and the character of the exposure-response relationships where effects were observed in this study suggests that these are due to chance." Although these data are not as reliable as those reported in the Gibbs *et al.* (1999 and Deschamps *et al.* (2001) studies, a NOAEL of 58 $\mu g/m^3$ can be assumed based on the likelihood of positive findings being due to chance.

Mergler *et al.* (1994) evaluated neurological effects of 74 Mn alloy workers and 74 matched controls exposed for an average of 16.7 years to respirable Mn air concentrations ranging from 1 to 1,273 $\mu g/m^3$, with an arithmetic mean of 122 $\mu g/m^3$. The authors evaluated the Mn-exposed workers as a group,

without dividing the study subjects into different exposure concentration categories, and found that the exposed workers performed more poorly on tests of motor function. Bouchard *et al.* (2006a,b) were follow-up studies of the same cohort after cessation of exposure, and some statistically significant neurological effects were observed, as shown on Table A.1. However, because of the wide range of exposure concentrations for this cohort, it is difficult to ascribe the observed effects to the mean of that exposure range, and therefore we conclude that this study does not provide a reliable basis, as compared to the Gibbs *et al.* (1999), Deschamps *et al.* (2001), and Young *et al.* (2005) studies discussed above for re-evaluation of the Mn RfC.

Finally, in a study by Bast-Petterson *et al.* (2004), a large number of neuropsychological tests were carried out on 100 Mn alloy plant workers and 100 controls (silicon and microsilica plant and titanium dioxide slag and pig iron plant workers) including tests for cognitive functions; motor tests; tests of motor speed, grip strength, coordination, and reaction time; and a questionnaire to evaluate self-reported neuropsychiatric symptoms. The average exposure concentration was 64 $\mu g/m^3$, ranging from 3 to 356 $\mu g/m^3$. Of these tests, three of eight motor tests (tremor tests) showed significant effects in the exposed *vs.* the control group. All cognitive tests and other neuropsychological tests were not significantly different, and there was no significant difference in self-reported neuropsychiatric symptoms between the two groups. Self-reported smoking habits did have an effect on tremor parameters. The lack of consistency among the tremor tests suggests that these findings are not robust for use in deriving an RfC.

Thus, the three most appropriate occupational studies for re-evaluation of the Mn RfC are the occupational studies by Gibbs *et al.* (1999) (NOAEL = 66 $\mu g/m^3$), Deschamps *et al.* (2001) (NOAEL = 57 $\mu g/m^3$), and Young *et al.* (2005) (NOAEL = 58 $\mu g/m^3$). These studies all provide NOAEL values (as opposed to LOAELs, so a UF is not needed for use of a LOAEL); are all chronic studies (greater than 7 years in duration); the values are consistent across the three studies, which provides additional support for the values; and individual exposure estimates are well-characterized in the studies.

A.2.2 Community-based epidemiology studies are not as reliable as occupational studies for use in re-evaluation of the Mn RfC

Several recent epidemiology studies were identified in which ambient Mn air concentrations were evaluated from residential communities in a mining district in Mexico (Santos-Burgoa *et al.*, 2001; Rodriguez-Agudelo *et al.*, 2006; Solis-Vivanco *et al.* 2009; Riojas-Rodriguez *et al.*, 2010) and near a

ferromanganese refinery in the US (Standridge *et al.*, 2008; Haynes *et al.* 2010). These community-based studies, also referred to as "ecological studies," examined potential associations between the manganese air concentrations in the communities and neurological effects in people living in those communities. Ecological studies examine groups of individuals and assess whether the overall occurrence of disease in the group correlates with the overall occurrence of exposure (Webster, 2007; Gordis, 2008). Importantly, because exposure data from these community-based studies were not individually based (*i.e.*, no personal air monitoring data were collected, as was done in the occupational studies discussed above), individual exposure concentrations are not known. Therefore, any observed neurological effects cannot necessarily be attributed to manganese air concentrations in the community. For this reason, as well as others described in more detail below, these studies do not provide reliable evidence of an association between Mn and potential health effects. In fact, all agency Mn inhalation toxicity criteria are based on the more reliable occupational studies, and not ecological studies (ATSDR, 2000, 2008; OEHHA, 2008; US EPA, 1993).

In the Mexican mining district study, where a 3-month average PM_{10} Mn concentration was found to be 0.42 $\mu g/m^3$, there were no statistically significant neurological effects for the majority of the motor control tests performed by Rodriguez-Agudelo *et al.* (2006) (1 out of 24 tests was borderline statistically significant), and the cognitive impairment tests performed by Solis-Vivanco *et al.* (2009) (1 out of 10 tests was borderline statistically significant). Rodriguez-Agudelo *et al.* (2006) observed a small association between position changes in hand movement and manganese air concentration and Solis-Vivanco *et al.* (2009) observed a small increase in poor performance on a digit-span attention test. Riojas-Rodriguez *et al.* (2010) observed intellectual functional impairment in a small group of children (n=79) in the Mexican mining district compared to children in nearby rural communities. However, there are factors other than the Mn air concentration that differ between children from the exposed and control communities that should be considered as part of interpretation of the observed effects in this study (*e.g.*, there is evidence of lower hemoglobin levels in the exposed *vs.* control groups. The mothers in the exposed group showed a lower performance on the Raven IQ test compared to controls, and more growth stunting was observed in exposed *vs.* control groups). These factors are called confounders, if found to potentially influence the observed effects, and would need to be considered for proper interpretation of the study results.

The study by Standridge *et al.* (2008) observed a positive association between Mn levels in hair and postural balance in a small group of residents (n=22) living near a ferromanganese refinery in Southern Ohio. The Mn air concentrations in this community were estimated to range from 0.1 $\mu g/m^3$ to

2 μg/m^3 total Mn. There are several problems with this study. Similar to the Mexican mining district studies, the exposures in this study are not well-characterized. In addition, the sample size is very small (the authors indicate that a study with a larger sample size is warranted), and the data are total suspended particulate (TSP) Mn as opposed to respirable manganese. Further, another study of the same residential community (Haynes *et al.* 2010) found that hair Mn levels were only associated with estimated Mn ambient air concentrations when genes for iron metabolism were included, suggesting that further research is needed into potential health effects in the community.

Several community-based studies were conducted from an area in southern Quebec where TSP 24-hour Mn ambient air concentrations ranged from 0.009-0.035 μg/m^3 (Baldwin *et al.* 1999; Beuter *et al.* 1999; Bowler *et al.* 1999; Mergler *et al.* 1999). Although the studies found some associations between increased levels of Mn in blood and neurological effects, increased Mn blood levels were also associated with increased consumption of green leafy vegetables and high-manganese cereals, and decreased serum iron levels. Similar to the community-based studies discussed above, the Mn exposures in these studies are not well-characterized. Given potential confounding effects related to diet and low iron levels, and the lack of good Mn ambient air exposure information for the individuals in the study, the observed effects cannot necessarily be attributed to Mn in ambient air.

Importantly, the exposure concentrations measured in the communities in these studies are very low compared to the exposure concentrations from the occupational studies discussed above. Although it is desirable to conduct studies with low exposures to Mn in air, the more reliable and numerous occupational studies consistently observed no adverse neurological effects at concentrations equal to or less than 60 μg/m^3. Therefore the reported effects in the community-based studies and the associated concentrations of Mn in air are not consistent with what has been observed in the more reliable occupational studies.[13] I conclude that the few observed effects in the community-based studies are not likely to be associated with the very low concentrations of Mn in air, and are more likely due to chance or confounding factors.

Because of the limitations in interpretation of the community-based studies, and the inconsistent observations in these studies compared to the more reliable occupational studies, the community-based studies are not reliable for re-evaluation of the Mn RfC. The preferential use of Mn occupational studies

[13] While it is conceivable that the general population may be more susceptible than worker populations to the effects of Mn, as discussed later in this report, there is no reliable evidence that the young, and other potentially sensitive populations, are significantly more susceptible to Mn than worker populations.

over ecological studies, for purposes of deriving toxicity criteria, has been demonstrated by several regulatory agencies (ATSDR, 2000, 2008; OEHHA, 2008; US EPA 1993).

A.2.3 Recent developmental data relevant to re-evaluation of the Mn RfC

Since 1993, several Mn inhalation studies have been conducted in animals to address the potential for developmental effects (Dorman *et al.*, 2005a,b; Erikson *et al.*, 2005; HaMai *et al.*, 2006). The lowest concentration where an effect was observed (decreased liver weights in male offspring at post natal day (PND) 63) was 500 $\mu g/m^3$ (Dorman *et al.*, 2005a). Liver weights at the high dose (1 mg/m^3) were not decreased at this time point, although they were decreased on PND 19. Since the decrease in liver weight does not appear to be dose-dependent and resolves at the highest dose by PND 45, this endpoint is of questionable significance and may not be treatment-related. The other Dorman study (Dorman *et al.*, 2005b) resulted in a NOAEL of 1 mg/m^3 based on a lack of clinical fetotoxicity in rats. Another study observed decreased expression of inflammation-related genes in the brains of rats exposed to 700 $\mu g/m^3$ during gestation or early adulthood (HaMai *et al.*, 2006).

Erikson *et al.* (2005) exposed neonatal rats to 0.05, 0.5, or 1 mg $MnSO_4/m^3$ during gestation through PND 18 (except for the period when parturition was expected to occur). Three weeks post-exposure, rats were sacrificed and metallothionein and glutamine synthetase mRNA levels, and glutamine synthetase and glutathione protein levels were measured in five brain regions. While changes were observed at some doses in some brain regions for all measured endpoints, the findings did not always exhibit a dose-response and were not always consistent in males in females. In addition, the changes in mRNA and protein transcription should not necessarily be considered adverse. The RfC, by definition, is based on a critical effect that considers adverseness, and may result in functional or structural impairment or be a precursor state to irreversible toxicity (US EPA, 1990). US EPA defines the "critical effect" as "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases" (US EPA, 2002). Therefore, the selected effect should be a critical effect on a causal pathway to disease. In determining a critical effect, it is important to acknowledge distinctions between adverse and adaptive effects. Adaptive effects may enhance an organism's performance, whereas an adverse effect impairs performance (Strawson *et al.*, 2004; Barnes and Dourson, 1988; Conolly, 2009; Goodman *et al.*, 2010). The toxicological significance of changes in mRNA and protein synthesis reported in the Erikson *et al.* (2005) study are unknown, could potentially be adaptive, and therefore should not be considered adverse.